Health-care-associated infection in a pediatric intensive care unit

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ABSTRACT

Introduction: Health-care-associated infection (HAI) is a major cause of concern in pediatric intensive care units (PICUs) all over the world and represents an important cause of mortality and financial burden for health-care systems. **Objective:** The objective of this study was to describe the epidemiologic profile of children with HAI. Methods: This was a prospective surveillance study conducted in a pediatric intensive care unit of a tertiary care hospital, India. Children, admitted to PICU between December 1, 2015, and November 30, 2016, were monitored for the development of bloodstream infection (BSI), ventilator-associated pneumonia, and urinary tract infection. **Results:** A total of 430 patients were admitted during the study period. Of 250 eligible patients, 15 children (6%) developed 19 episodes of HAI with patient prevalence of six infections per 100 patients. Only Gram-negative bacteria were identified, *Klebsiella pneumoniae* was the most common organism (68.42%). Bloodstream was the most common site of HAI (n=11, 58%) followed by respiratory tract (n=6, 32%) and urinary tract (n=2, 10%). In a univariate analysis, survivors of cardiac arrest or trauma, malnourished children had an increased risk of acquiring HAI. The presence of lymphopenia (≤1000/mm3), hypercarbia (Pco_2 >65 mmHg), sodium imbalance (<130 meq/L or >150 meq/L), organ dysfunctions, and length of stay before acquiring infection was all associated with an increased risk of developing HAI ($p<0.05$). **Conclusions:** BSI is the most common HAI and only Gram-negative organisms were identified in our unit.

Key words: *Bloodstream infection, Health-care-associated infection, Urinary tract infection, Ventilator-associated pneumonia*

Health-care-associated infection (HAI) is defined as a localized or systemic condition occurring as a consequence of an adverse reaction to the presence of an infectious agent(s) or its toxin(s). Infection must not be present or incubating at the time of admission. They also include infections acquired in the hospital but manifest after discharge [1]. HAIs represent an important cause of mortality and financial losses for health systems [2]. There is a scarcity of information regarding estimates of the burden of HAIs in developing countries. Unlike developed counties, there is no national surveillance system for HAI in India. We performed a prospective cohort single-center study to describe the epidemiology of HAIs and identify the etiological organisms and risk factors associated with the development of HAIs in the pediatric intensive care unit (PICU) from a developing country. We aim to use the results to identify risk factors for developing HAI and develop intervention strategies to deal with HAIs.

METHODS

A prospective study was conducted in PICU at a multispecialty teaching hospital in Eastern India, from December 2015 to November 2016. A study was approved by the institutional ethics committee. Our PICU has eight beds and has facilities for invasive and non-invasive hemodynamic and respiratory monitoring. On an average, nearly 500 patients are admitted annually in our unit. All children ≤12 years of age, who were admitted to PICU and stayed for >24 h, were eligible for enrolment in the study. Patients with immunodeficiency (congenital or acquired) and/or those with neutropenia (neutrophil count <500/mm^3) were excluded from the study.

HAIs including bloodstream infections (BSIs), ventilator-associated pneumonia (VAP), and urinary tract infections (UTI) were defined according to the Centers for Disease Control and prevention defining criteria [1].

Laboratory-confirmed BSI is diagnosed when it meets at least one of the following criteria: (1) Patient has a recognized pathogen cultured from ≥1 blood cultures and organism cultured from blood is not related to an infection at another site. (2) Patient has at least one of the following signs or symptoms: Fever (>38°C), chills, or hypotension and signs and symptoms and positive laboratory results are not related to an infection at another site and common skin contaminant (i.e., diphtheroids [*Corynebacterium* spp.], *Bacillus* [not anthracis] spp., *Propionibacterium* spp., coagulase-negative staphylococci [including *Staphylococcus epidermidis*], viridans group streptococci, *Aerococcus* spp., and *Micrococcus* spp.) is cultured from two or more blood cultures drawn on separate occasions. (3) Patient ≤1 year of age has at least one of the

following signs or symptoms: Fever (>38°C, rectal), hypothermia (<37°C, rectal), apnea, or bradycardia and signs and symptoms and positive laboratory results are not related to an infection at another site and common skin contaminant is cultured from two or more blood cultures drawn on separate occasions [1].

VAP was defined as pneumonia in persons who had a device to assist or control respiration continuously through a tracheostomy or by endotracheal intubation within the 48-h period before the onset of infection, inclusive of the weaning period [1].

To diagnose a symptomatic UTI, it must meet at least one of the following criteria: (1) Patient has at least one of the following signs or symptoms with no other recognized cause: Fever (>38°C), urgency, frequency, dysuria, or suprapubic tenderness and patient has a positive urine culture, i.e., $\geq 10^5$ microorganisms per cc of urine with no >2 species of microorganisms. (2) Patient has at least two of the following signs or symptoms with no other recognized cause: Fever (>38°C), urgency, frequency, dysuria, or suprapubic tenderness and at least one of the following: (a) Positive dipstick for leukocyte esterase and/or nitrate. (b) Pyuria (urine specimen with ≥10 white blood cell [WBC]/mm^3 or ≥3 WBC/high-power field of unspun urine). (c) Organisms seen on Gram's stain of unspun urine. (d) At least two urine cultures with repeated isolation of the same uropathogen (Gram-negative bacteria or *Staphylococcus saprophyticus*) with $\geq 10^2$ colonies/mL in non-voided specimens. (e) $\leq 10^5$ colonies/mL of a single uropathogen (Gram-negative bacteria or *S. saprophyticus*) in a patient being treated with an effective antimicrobial agent for UTI. (f) Physician diagnosis of UTI. (g) Physician institutes appropriate therapy for UTI. (3) Patient ≤1 year of age has at least one of the following signs or symptoms with no other recognized cause: Fever (>38°C rectal), hypothermia, and at least one of the following: (a) Positive dipstick for leukocyte esterase and/or nitrate. (b) pyuria (urine specimen with ≥10 WBC/mm^3 or ≥3 WBC/high-power field of unspun urine). (c) organisms seen on Gram's stain of unspun urine. (d) at least two urine cultures with repeated isolation of the same uropathogen (Gram-negative bacteria or *S. saprophyticus*) with $\geq 10^2$ colonies/mL in non-voided specimens. (e) $\leq 10^5$ colonies/mL of a single uropathogen (Gram-negative bacteria or *S. saprophyticus*) in a patient being treated with an effective antimicrobial agent for UTI. (f) Physician diagnosis of UTI. (g) Physician institutes appropriate therapy for UTI [1].

An asymptomatic bacteriuria must meet at least one of the following criteria: (1) Patient has had an indwelling urinary catheter within 7 days before the culture and patient has a positive urine culture, i.e., $\geq 10^5$ microorganisms/cc of urine with no >2 species of microorganisms and patient has no fever (>38°C), urgency, frequency, dysuria, or suprapubic tenderness. (2) Patient has not had an indwelling urinary catheter within 7 days before the first positive culture and patient has had at least two positive urine cultures, i.e., $\geq 10^5$ microorganisms per cc of urine with repeated isolation of the same microorganism and no >2 species of microorganisms and patient has no fever (>38°C), urgency, frequency, dysuria, or suprapubic tenderness [1].

At admission, patient-related clinical and laboratory data were recorded, which included the following details: Age, sex, source of admission (direct or referred from other hospital), history of trauma, nutritional status, and protein-energy malnutrition (PEM) as defined according to the Indian Academy of Pediatrics classification of PEM [3], Glasgow Coma Scale (GCS), blood pressure, hemoglobin, lymphocyte count, platelet count, pH, base excess, serum lactate, PaO_2/FiO_2, serum electrolytes, prothrombin time/international normalized ratio, activated prothrombin time, serum creatinine, total serum bilirubin, and alanine transaminase.

Severe anemia was defined as Hb <7 g/dl in children aged <5 years and Hb <8 g/dl in children aged 5–12 years [4]. Lymphopenia, thrombocytopenia, acidosis, hypercarbia, hyperlactatemia, and organ system dysfunction were defined based on criteria for organ dysfunction [5]. Sodium imbalance was defined as Na <130 or >150 mEq/L. Data related to length of PICU stay, device utilization, invasive procedures, surgical intervention, and events such as cardiac arrest and blood component transfusion were recorded. The common HAIs in PICU, i.e., VAP, BSI, and UTI were included in the study.

Statistical analysis was performed where baseline characteristics were presented as mean ± SD or percent. Categorical variables were compared using Chi-square or Fisher's exact test as appropriate. Proportions were compared using the Z-test. For comparison of paired proportions, McNemar test was applied. Student's t-test was applied to analyze parametric data.

RESULTS

A total of 430 patients were admitted during the study period. Of 430 admissions, 250 patients were eligible for study as 178 children were transferred out of PICU in <24 h and two children had immunodeficiency. The HAI patient prevalence in our cohort is six infections per 100 patients. The mean age of enrolled patients was 47.93±45.52 months. Male-female ratio was 1.5:1. Of the 19 episodes of HAI, BSI was the most common HAI (n=11; 57.9%) in our study cohort followed by VAP (n=6; 31.6%) and UTI (n=2; 10.5%).

The length of stay in the PICU before developing HAI was 7.53±4.24 days. The total length of PICU stay was longer in the children with HAI (mean 22.81±22.27 days) in comparison with those without HAI (mean 5.26±4.68 days). Patients have stayed for a minimum of 3 days and a maximum of 14 days before developing HAI. A single patient's PICU stay was for a period of 43 days in PICU before developing HAI.

During the study period, PICU had 764 central line days, 1017 urinary catheter days, and 680 ET days. The mean number of days of the urinary catheterization in HAI group and non-HAI group was 15.2±9.83 and 3.36±3.47 days, respectively. The mean number of days of the endotracheal/tracheostomy tube in HAI group and non-HAI group was 17.73±23.87 and 2.2 ±3.93 days, respectively. The mean number of days of the central line in HAI group and non-HAI group was 16.4±12.55 and 2.2±3.65 days, respectively. Thus, expressed in terms of device days, BSI was

14.4/1000 central line days, VAP was 8.82/1000 ET days, and UTI was 1.97/1000 urinary catheter days.

Table 1 shows the univariate analysis of differences in admission and baseline characteristics of our cohorts of children who developed HAI and who did not develop HAI. In univariate analysis, survivors of cardiac arrest or trauma, malnourished children had an increased risk of acquiring HAI. The presence of lymphopenia (≤1000/mm^3), hypercarbia (Pco_2 >65 mmHg), sodium imbalance (<130 meq/L or >150 meq/L), and organ dysfunctions was all associated with an increased risk of developing HAI ($p<0.05$) which indicates increased severity of illness at admission. However, the presence of infection or sepsis at admission did not have an increased risk of developing HAI.

Table 2 shows organisms identified. There were a total of 19 instances of HAI. In our cohort, only Gram-negative bacteria were identified representing hospital-acquired bacterial ecology. *Klebsiella pneumoniae* was the most common organism.

Antibiotic sensitivity pattern was observed as follows: *K. pneumoniae* causing BSI were sensitive to tigecycline (89%) and colistin (89%) followed by cotrimoxazole (78%) and meropenem, amikacin, cefepime, piperacillin-tazobactam, and cefoperazone-sulbactam (22.22%). Both strains of *Enterococcus* causing BSI were sensitive to tigecycline, linezolid, and vancomycin. *K. pneumoniae* causing VAP (n=4) were sensitive to tigecycline (75%) followed by colistin (50%) and cotrimoxazole (50%) and to cefepime and cefoperazone-sulbactam (25%). Two *Acinetobacter* strains in VAP were sensitive to tigecycline and colistin followed by meropenem (50%). Both *Escherichia coli* strains in UTI were sensitive to colistin, meropenem, piperacillin-tazobactam, and cefoperazone-sulbactam. One of them was sensitive to cefepime, amikacin, and nitrofurantoin.

DISCUSSION

HAI is a major cause of concern in PICUs. We performed a prospective cohort study to describe the epidemiologic profile of HAIs and to determine the risk factors in our unit.

The HAI patient prevalence in our cohort is six infections per 100 patients. The overall HAI prevalence in critically ill children in our study is comparable to the reported HAI rate of 6–8/100 patients of PICU from developed countries [6,7]. There is a paucity of data from developing countries and it is believed that HAI prevalence may be higher in developing countries [8,9]. Murni *et al*. reported HAI prevalence of 45% at a single center in a developing country which came down to 17% after implementing infection control program [10]. Our rate is not higher than western data as speculated; it may be due to difference in clinical profiles of admitted patients in our unit. Patient admitted to PICUs from developed countries may be sicker as they get many patients referred from secondary care hospitals with high dependency units for PICU care.

BSI was the most common HAI (57.9%) in our study cohort. According to the National Nosocomial Infection Surveillance System (1999), the most common sites of infections were bloodstream (28%) followed by the lower respiratory tract (21%) and urinary tract (15%) [6]. A study conducted by Singh-Naz *et al.*, lower respiratory tract was the most common sites of infections (35%) followed by BSI (21%) and UTI (16%) [7]. Dramowski *et al.* reported VAP to be the most common HAI in their cohort from PICU followed by UTI and BSI [11]. Most frequent types of HAIs identified by Aktar *et al.* in a cohort consisting of patients both in PICU and inpatient ward, were BSI, VAP, catheter-associated BSI, and UTI. As their cohort included both pediatric

Table 1: Admission and baseline characteristics of patients with and without HAI

Characteristics	With HAI (n=15)	Without HAI (n=235)	p-value
Trauma	5	15	0.0031*
Cardiac arrest	4	6	0.0015*
Malnutrition	10	81	0.0253*
Anemia (<7 mg/dl)	2	23	0.6515
Lymphopenia (<1000/mm^3)	3	5	0.0082*
Thrombocytopenia (<100,000/mm^3)	2	30	0.2242
Referred from other hospitals	4	18	0.0323*
Chronic illness	2	33	1.000
Surgical intervention	4	58	0.7564
Infection	2	7	0.0948
Acidosis (base deficit >5 meq/L)	4	31	0.2384
Hypercarbia (PCO_2 >65 mmHg)	3	11	0.0427*
Hyperlactatemia (>4 mmol/L)	1	23	1.000
Hyponatremia/hypernatremia (<130 or >150 meq/L)	8	50	0.0088*
Hypernatremia (>150 meq/L)	3	6	0.0119*
Hyponatremia (<130 meq/L)	5	44	0.1816
Hypokalemia/hyperkalemia (<3 or >5.5 meq/L)	1	26	1.000
Hypocalcemia/hypercalcemia (<8 or >12 meq/L)	6	43	0.0845
Organ dysfunction	14	111	<0.0001*

HAI: Health-care-associated infection,*marked has significant p<0.05

Table 2: Organisms isolated in HAI

HAI (n=19)	Organism (%)
BSI (n=11; 57.9%)	*K. pneumoniae* (n=9; 81.8)
-	*Enterobacter* species (n=2: 18.2)
VAP (n=6; 31.6%)	*K. pneumoniae* (n=4; 66.7)
-	*Acinetobacter* species (n=2; 33.3)
UTI (n=2; 10.5%)	*Escherichia coli* (n=2; 100)

HAI: Health-care-associated infection; BSI: Bloodstream infection; VAP: Ventilator-associated pneumonia; UTI: Urinary tract infection, *K. pneumonia: Klebsiella pneumoniae*

inpatient and PICU patients, they had high prevalence of BSI not associated with catheter [12]. All of the BSIs in our cohort were associated with central line. Disproportionately higher prevalence of BSI means that we need to handle central lines more carefully and is an area for training of our health care workers.

In our cohort, only Gram-negative organisms were identified to be causative organisms for HAIs. We did not have Gram-positive infection in our cohort. *K. pneumoniae* (82%) was the most common organism causing BSI followed by *Enterobacter* species (18%). This is in contrast to studies from developed countries which have shown predominance of Gram-positive organisms [12]. Our study is similar to that of Lakshmi *et al.* from a tertiary care hospital in India, which showed Gram-negative predominance [13]. *K. pneumoniae* (67%) was the most common organism causing VAP followed by *Acinetobacter* species (n=2; 33%). *E. coli* were only organism isolated from urine.

Of late, there has been gradual declining trend in acquiring *Staphylococcus* species related HAI with concurrent upward trend in Gram-negative organisms related HAI with no significant change in overall HAI incidence [14,15]. This has a bearing on the choice of antibiotics used for empirical treatment of HAI at our institution. Clearly, there is no need to cover empirically for Gram-positive organisms at our center while treating HAI. Resistance to the third-generation cephalosporin and sensitivity only to tigecycline and colistin in some strains and resistance to carbapenems is a sign of impending danger of pan-resistant organisms where no antibiotic would work. de Kraker *et al.* have reported third-generation cephalosporin-resistant *E. coli* causing significant excess mortality and prolonged hospital stay resulting in a substantial extra burden on the health-care delivery system [16].

Risk factors for the development of HAI in our cohort were identified. Patients who were admitted directly to PICU had less risk of developing infection compared to those who were transferred from other hospitals. Cardiac arrest survivors had an increased risk for acquiring HAI. Risk of infection increased with malnutrition, increasing age, lower lymphocyte count, sodium imbalance, and higher CO_2 [7]. Average length of stay was longer in the children with HAI in our cohort. Length of stay before developing infection is a risk factor for acquiring HAI [7,12,13]. These risk factors are known and reported from earlier studies as well [7,12,13,17].

Cardiac arrest is associated with increased odds of developing nosocomial infections [17]. In our cohort, survivors of cardiac arrest had increased risk of developing HAI (40% vs. 1.7%, p=0.0015). It has been proposed that regurgitation during CPR leading to aspiration pneumonia; breach in intestinal wall integrity secondary to ischemia-reperfusion injury may be contributory factors to the acquisition of infection. Furthermore, cardiac arrest survivors are likely to be on invasive mechanical ventilation and invasive hemodynamic monitoring for prolonged period, leading to an increased risk for infections [6]. In addition, we suspect that there is breach of infection control measures during resuscitation procedure that may contribute to increased incidence.

Trauma is known to increase HAI risk and was associated with almost 2-fold increased odds of developing infections [7,17]. In our cohort, children with trauma had an increased risk of developing HAI. Trauma and associated tissue injury leads to destruction of physical barrier against bacterial and fungal infections; skin lacerations lead to direct infection with skin commensals and soil flora [17-20]. Our study also showed that the risk of developing HAI was higher in patients who had lymphopenia at admission. Lymphopenia is the most common risk factor identified in the development of nosocomial infection [17]. Increased risk of infection in patients with lymphopenia is postulated to be due to stress response causing apoptosis of lymphocyte and immune dysfunction [17].

The present study is limited by its small number of HAI due to which multivariate analysis is not done. Being a single-center study, our results may not be applicable to other units as our patient profile, medical practice, and bacterial ecology may be different.

CONCLUSIONS

BSI is the most common HAI. Only Gram-negative organisms were identified in children with HAI. Survivors of cardiac arrest, trauma, and children with lymphopenia have an increased risk of developing HAI.

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